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Case Report

Fosphenytoin-induced purple glove syndrome: A case report

Joseph W. Newman[a], Joseph R. Blunck[b,*], Ronald K. Fields[a], John E. Croom[a]

[a] Department of Neurology, Epileptology Division, Saint Luke's Hospital, Kansas City, M0, 64111, USA
[b] Department of Pharmacy, Neuroscience Division, Saint Luke's Hospital, Kansas City, M0, 64111, USA

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ABSTRACT

Background: Purple glove syndrome (PGS) is a poorly understood severe adverse drug reaction that is typically associated with intravenous phenytoin administration. Although fosphenytoin is thought to circumvent this risk of PGS, we reveal a rare case of PGS in a patient treated with fosphenytoin therapy.

Case summary: A 71-year-old male with history of epilepsy was admitted for seizures and traumatic brain injury and intravenous fosphenytoin and levetiracetam were initiated. The patient continued to have seizure activity on continuous electroencephalography for which fosphenytoin dosing was increased with subsequent seizure control. Serum phenytoin levels became elevated with a total level reaching as high as 25.8 ug/mL. Three days into fosphenytoin therapy he developed PGS in both hands. Causation was assessed with the Naranjo adverse drug reaction algorithm that suggested fosphenytoin was probably the cause of PGS. Ten days after discontinuing the fosphenytoin and administering a 7-day course of methylprednisolone, the purple glove syndrome completely resolved.

Conclusion: Early recognition and emergent management of PGS are key for optimal recovery. Although fosphenytoin has a significantly reduced risk of associated PGS compared to phenyotin, increased awareness for fosphenytoin-induce PGS can accelerate intervention and minimize morbidity of this rare yet detrimental adverse reaction.

Introduction

Purple glove syndrome (PGS) is an atypical adverse drug reaction that can occur after the administration of intravenous phenytoin. Although definitions of PGS vary, it has been loosely defined as signs and symptoms of progressive edema, discoloration, and pain that occurs following administration of intravenous phenytoin [1]. The characteristics of this syndrome occur in three different stages: appearance, progression, and resolution of symptoms. These characteristics usually occur in the upper extremity, distal to the intravenous access site. The first stage occurs within 12 h after infusion of intravenous phenytoin, where a dark purple-bluish discoloration of the skin appears adjacent to the site that the infusion took place. Approximately 12–16 h later, worsening discoloration and edema are present and the severity becomes more apparent [1]. Pain is usually present with all stages, and in rare cases, PGS may progress to necrosis of the distal extremity, ischemia, vascular compression, or compartment syndrome requiring surgical intervention. During the healing stage, edema resolves and discoloration recedes from the outer edges to toward the original site of injury [1].

The US Food & Drug Administration (FDA) and Pfizer safety analysts identified several spontaneous postmarketing reports of possible PGS from fosphenytoin, but every case lacked meaningful clinical details that would enable accurate assessment of the clinical course [2,3]. No published case reports have been identified describing PGS with fosphenytoin, and no cases have been identified in clinical trials or observational studies. To our knowledge, this is the first fully documented case report of fosphenytoin-induced PGS with complete clinical neurological assessment, dermatological consultation, treatment, and objective data to support the diagnosis.

Case report

A 71 year-old, 80 kg male with a history of intractable epilepsy following a remote brain injury in 2001 who was initially treated with Dilantin 400 mg PO nightly which was eventually discontinued for unknown reasons. Over the years, he would intermittently present with breakthrough seizures requiring admission with IV fosphenytoin for treatment. In 2015, he was admitted for breakthrough seizures secondary to bilateral intracranial hemorrhages. The following day (day 2 of 20), continuous EEG revealed multiple discharges that suggested gradual worsening of epileptiform activity. Subsequently, an

* Corresponding author at: Department of Pharmacy, Division of Neuroscience, Saint Luke's Hospital, 4401 Wornall Rd, Kansas City, M0, 64111, USA.
E-mail address: jblunck@saint-lukes.org (J.R. Blunck).

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intravenous bolus of fosphenytoin 1000 mg IV followed by 100 mg PE every 8 h, and levetiracetam 500 mg twice daily were initiated. Peripheral intravenous catheters were present in both left and right forearms. The rate of administration for fosphenytoin is not documented, however, the instructions specify the rate of administration was not to exceed a rate of 150 mg PE/minutes while infusing. An initial serum total phenytoin level of 15.2 ug/mL was drawn seven hours after the first bolus of fosphenytoin. Intermittent bouts of partial status epilepticus were identified on day 3, warranting a 500 mg bolus of IV fosphenytoin. A random phenytoin level of 15.0 ug/mL and free level of 2.7 ug/mL (send out lab resulted the following day), and albumin level of 3.0 g/dL were recorded early on day 4. EEG demonstrated frequent subclinical seizures and occasional status epilepticus was seen leading to the administration of a 500 mg bolus of fosphenytoin, and increasing the scheduled fosphenytoin to 160 mg PE every 8 h. The levetiracetam was also increased to 1000 mg every 12 h. The patient was concomitantly being treated for suspected sepsis and aspiration pneumonia. Approximately 3 days (day 5) after the initiation of fosphenytoin, the patient developed increased redness of his chest, arms, legs, face, and creases of palms. In addition, several raised round lesions of the arms were noted. A phenytoin level was drawn and revealed an elevated value of 25.8 ug/mL. In addition, the albumin level was 2.1 g/dL. There was one more dose of fosphenytoin 160 mg PE IV given prior to its discontinuation on day 6. Dermatology noted bilateral edematous purpuric hands, right greater than left (Fig. 1), and diagnosed the patient with PGS. There was no evidence of toxic epidermal necrolysis or Stevens-Johnson syndrome. Intravenous methylprednisolone 60 mg every 8 h was initiated and both peripheral IV catheters were discontinued. The edematous purpura began improving on day 8. However, it was noted that there was diffuse purple discoloration of the hands with the upper chest displaying a significant erythematous rash. The methylprednisolone dose was tapered off after seven days of therapy. By day 16, the patient's hands were desquamating and the erythema was continuing to improve with mild edema still present. Corresponding phenytoin levels were 5.1 ug/mL, and continued to gradually trend downwards until it reached 3.1 ug/mL at discharge (day 20). Dramatic resolution of PGS occurred after stopping fosphenytoin and starting intravenous steroids. Ergo, the most logical explanation for the patients PGS is the use of IV fosphenytoin. The correlation between the therapeutic events relating to the total serum phenytoin levels (Fig. 2) gives additional support that fosphenytoin was the probable cause of PGS. In addition, the Naranjo Adverse Drug Reaction Probability Scale (Table 1), designed as a technique to monitor drug reactions, was used on this patient [4]. A score of 7 was given which, based on the timing of the reaction, indicates that fosphenytoin was likely the cause of PGS.

Discussion

Fosphenytoin is phosphate ester pro-drug of phenytoin that came to the US market in 1996 and was designed to circumvent infusions complications associated with phenytoin [2,5]. Once administered, fosphenytoin is rapidly hydrolyzed by plasma esterases to phenytoin which is approximately 90% protein bound. Patients with hypoalbuminemia can have an elevated amount of phenytoin free levels. Phenytoin then acts by stabilizing neuronal membranes by altering sodium concentrations and ultimately decreasing seizure activity. The saturable (Michaelis-Menten) metabolism of phenytoin can lead to non-linear level elevation and a prolonged elimination half-life [5]. Serious adverse reactions to IV fosphenytoin are severe hypotension, cardiac

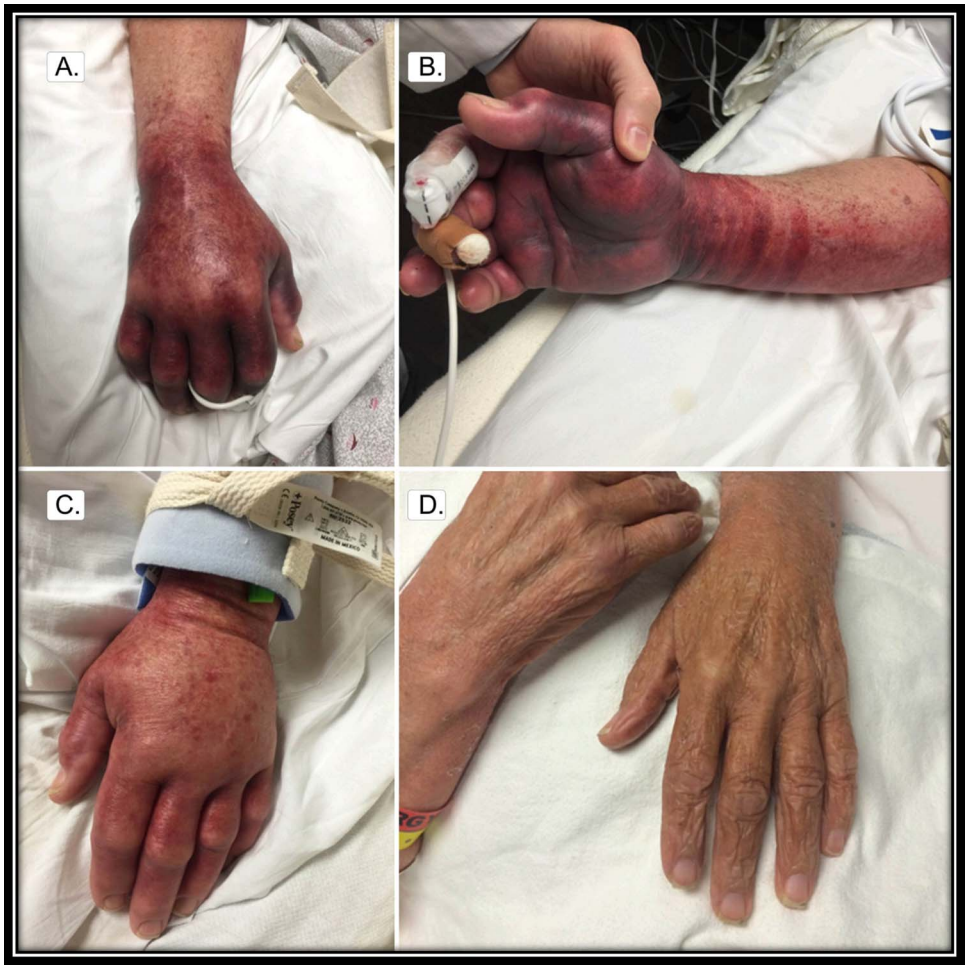

Fig. 1. Purple Glove Syndrome.
Purple glove syndrome characterized by purplish-black hand discoloration accompanied by edema (Panels A, B, and C). Purple glove syndrome resolved (Panel D) one week following discontinuation of fosphenytoin.